APPENDIX B

**Jackson Heart Study Manuscript Proposal Form**

**Please read JHS Publications & Presentations Guidelines before completing this proposal form.**

**JHS P #**

**Date of Submission: \_\_\_ (mm/dd/yyyy) Date of Approval: \_\_\_ (mm/dd/yyyy)**

**PART I. OUTLINE OF PAPER**

**1.  Title Information**

a. Proposal Title: (Please include the phrase “Jackson Heart Study” whenever possible)

**Number of Blood Pressure Readings on Ambulatory Monitoring and Risk for Cardiovascular Disease and All-cause Mortality: The Jackson Heart Study**

b. Abbreviated Title: (50 characters)

**Number of ABPM readings and risk for CVD and mortality**

c. Suggested key words:

Ambulatory Blood Pressure Monitoring, cardiovascular disease risk, mortality

**2.**   **Lead Author Name:  Rikki M. Tanner**

Institutional Affiliation**:** University of Alabama at Birmingham School of Public Health

Address: 1665 University Blvd, Suite 217J, Birmingham, AL 35233

Telephone:       205-934-5304      Fax:

Email:     rmdeitz@uab.edu

**3.**   **Co-authors, Contact Information, and Responsibilities:** (Proposed co-authors,

Email address and/or telephone numbers and proposed responsibilities.  Examples of responsibilities include design and concept of study, statistical analysis, data acquisition, methodological expertise, funding acquisition, literature review. Also indicate specific writing assignments including: introduction methods, results, discussion, preparation of tables and figures. Items not assigned to a co-author are assumed to be the responsibility of the lead author. Corresponding author should also be identified if it is not to be the lead author.)

|  |  |  |
| --- | --- | --- |
| **Name** | **Contact Information** | **Responsibilities** |
| Corey K. Bradley | cb3543@cumc.columbia.edu | Design and concept of study, interpretation of data, critical revision of the manuscript |
| Byron C. Jaeger | bjaeger@wakehealth.edu | Design and concept of study, analysis and interpretation of data, critical revision of the manuscript |
| S. Justin Thomas | [sjthoma@uabmc.edu](mailto:sjthoma@uabmc.edu) | Design and concept of study, interpretation of data, critical revision of the manuscript |
| Shakia T. Hardy | sthardy@uab.edu | Design and concept of study, interpretation of data, critical revision of the manuscript |
| M. Ryan Irvin | irvinr@uab.edu | Design and concept of study, methodological expertise, interpretation of data, critical revision of the manuscript |
| Daichi Shimbo | ds2231@cumc.columbia.edu | Design and concept of study, methodological expertise, interpretation of data, critical revision of the manuscript |
| Joseph E. Schwartz | jes2226@cumc.columbia.edu | Design and concept of study, methodological expertise, interpretation of data, critical revision of the manuscript |
| Paul Muntner | [pmuntner@uab.edu](mailto:pmuntner@uab.edu) | Design and concept of study, methodological expertise, interpretation of data, critical revision of the manuscript |

**4.**   **Non-JHS Lead Authors:** Non JHS Lead authors are required to have a JHS co-author and primary contact person (indicate with an asterisk). Non-JHS Lead Authors are encouraged to visit the JHS Website

<http://jhs.jsums.edu/jhsinfo> or [www.nhlbi.nih.gov/about/jackson/](http://www.nhlbi.nih.gov/about/jackson/) for information on JHS investigators. The JHS Steering Committee may nominate additional authors if special expertise for interpreting JHS data is needed)

**5**. **Brief Overview**: In 250 words maximum, provide a brief overview of the proposal including the nature of the problem to be addressed, scientific relevance, objectives/aims, research question/hypotheses, and methods/analytical plan. This overview will be posted on the internal JHS website.

Studies demonstrate that out-of-office blood pressure (BP), measured with ambulatory BP monitoring (ABPM), has a stronger association with cardiovascular disease (CVD) events and mortality compared to office BP. It remains unclear if this is due to more BP readings being available on ABPM, providing a better estimate of mean BP compared to office measurements or if it is due to the greater ecological validity of BP on ABPM. Greater ecological validity refers to readings on ABPM being taken in individuals’ usual environment while they are engaged in typical, everyday activities). We hypothesize that mean systolic BP (SBP) and diastolic BP (DBP) will be associated with incident CVD events and all-cause mortality, and the associations will be stronger for daytime values on ABPM versus those obtained in the office setting, holding the number of BP measurements fixed for both BP measurement modalities. We will include Jackson Heart Study participants without a history of CVD at baseline with follow-up data for CVD events and all-cause mortality who have at least 20 daytime BP measurements on ABPM, in accordance with the 2021 European Society for Hypertension guideline and 2 office BP measurements. We will compare the associations between mean office BP and ABPM-derived daytime BP with incident CVD events and all-cause mortality, separately, holding the number of BP measurements fixed at 2 for both modalities. We will recalculate the associations between daytime BP with CVD events and all-cause mortality, using the average of 3 to 20 BP readings from the ABPM recording.

**6.**   **Background/Rationale (**Include the relevance of this proposal to African Americans

and justify the need for the JHS cohort to answer the research question**):**

Blood pressure (BP) is a major risk factor for cardiovascular disease (CVD) and all-cause mortality. Measuring BP in the office setting has been the standard approach for the diagnosis and management of hypertension. BP fluctuates and office BP readings may not reflect a person’s BP over time. Furthermore, office BP does not account for variation in BP throughout the day. Ambulatory BP monitoring (ABPM) typically measures BP every 15 to 30 minutes throughout the day and night and thus, quantifies BP outside of the office setting. ABPM provides a more precise measure of true BP compared to measurements obtained during a single office visit and can detect circadian changes and BP variability within different environments and emotional states. Additionally, when used in conjunction with office BP, ABPM is an effective tool for identifying phenotypes such as white-coat, masked, and nocturnal hypertension1. Numerous studies and systematic reviews indicate that out-of-office BP, measured with ABPM, has a stronger association with CVD events and mortality compared to office BP.3-5 It remains unclear whether out-of-office BP has a stronger association with CVD and mortality than office BP because the large number of readings obtained with ABPM provides a more reliable estimate of mean ABP or because of the greater ecological validity of BP assessed by ABPM compared to office BP (i.e., out-of-office BP being less susceptible to a white-coat effect and/or better reflecting an individual’s BP during everyday life).

**7.**   **Research Hypotheses:**

Hypothesis 1: The associations with incident CVD events and all-cause mortality will be stronger for daytime BP derived by ABPM versus in the office setting, holding the number of BP measurements fixed.

**Specific Aims:**

**Aim 1:** Compare the associations of mean office SBP and DBP versus mean daytime systolic and diastolic on ABPM with incident CVD events and all-cause mortality, separately, holding the number of measurements fixed at 2 for both modalities.

**Aim 2a:** Determine the association of daytime SBP and DBP with incident CVD events and all-cause mortality, separately, using the average of the first 20 consecutive ABPM readings to define daytime SBP and DBP. In a secondary analysis, we will use the average of 20 randomly selected ABPM readings to define daytime SBP and DBP.

**Aim 2b:** Recalculate the associations of daytime SBP and DBP with CVD and all-cause mortality, using the average of the first 3 to 19 consecutive SBP and DBP readings from the ABPM recording. In a secondary analysis, we will use the average of 3 to 19 randomly selected ABPM readings to define daytime SBP and DBP.

**8.**   **Data:** (Visits and variables to be used, sample inclusions/exclusions)

Study sample: Jackson Heart Study participants with follow-up data for CVD and mortality who have at least 20 daytime SBP and DBP readings on ABPM, 2 office SBP and DBP measurements at baseline, and without a history of CVD at baseline.

**Variables**

Age [AGE]

Sex (M/F) [SEX]

Body Mass Index [BMI]

Diabetes [DIABETES]

Education level [EDUCATION]

Smoking status [CURRENT SMOKER and EVERSMOKER]

eGFR [GFR01CC]

Urine albumin and creatinine [CREATININEUSPOT and ALBUMINUSPOT]

CBP (systolic and diastolic) [SBPC19 and SBPC20]

ABP (systolic and diastolic) [ABDA4 and ABDA6]

Time of ABPM reading (Hours) [ABDA8]

Time of ABPM reading (Minutes) [ABDA9]

Antihypertensive medication use [msra30a]

History of myocardial infarction [MIHX]

History of coronary heart disease [CHDHX]

History of stroke [STROKEHX]

History of CVD [CVDHX]

Follow-up time [yearsfromv1]

Incident coronary heart disease [CHD, HARDCHD]

Coronary heart disease follow-up time [YEARS, HARDYEARS]

Incident heart failure [HF]

Heart failure follow-up time [YEARS]

Incident stroke [STROKE]

Stroke follow-up time [YEARS]

All-cause mortality [STATUS]

**Dependent Variables (Exam 1)**

CVD events will be defined as incident stroke, coronary heart disease, or heart failure event during follow-up. Of note, heart failure outcomes are not available before 2005.

All-cause mortality will be defined as death from any cause during follow-up.

**9.**   **Brief Statistical Analysis Plan and Methods:**(Including power calculations, if necessary.)

Participant characteristics will be summarized using means (± standard deviations) and percentages for continuous and categorical variables, respectively. The number and percent of missing values will be reported in descriptive tables, and multiple imputation will be applied if the proportion of participants with missing baseline data exceeds 5%. The analyses below will first be conducted for SBP and then repeated for DBP. Similarly, analyses will first consider incident CVD events as the outcome and then be repeated using all-cause mortality as the outcome. Mean office SBP will be defined as the average of the 2 SBP measurements taken at the baseline examination.

We will use Cox regression to estimate the association between daytime SBP on ABPM and CVD events. Cox regression models will be fit under three specifications:

Model 1: adjustment for age and sex

Model 2: adjustment for age, sex, education, body mass index, diabetes, smoking status, alcohol use, albumin to creatinine ratio, reduced eGFR, antihypertensive medication use, and a history of myocardial infarction or stroke

Model 3: adjustment for the variables in Model 2 with additional adjustment for office SBP and DBP.

**Comparing daytime SBP versus office SBP**. We will fit two Cox regression models, with one including daytime SBP using the mean of 2 ABPM readings and the other including the mean of two office SBP readings. Using bootstrap resampling, we will estimate a 95% confidence interval for the difference in the hazard ratios between mean daytime SBP using 2 readings versus office SBP. Adjustment will be performed for the covariates in Model 3. If the confidence interval for this difference does not contain 0, it indicates that one SBP measurement approach is more closely associated with CVD than the other, suggesting better performance for CVD risk stratification. We will also estimate using bootstrap resampling the difference in C-statistics between these two Cox regression models to assess whether one SBP measurement approach produces a model that is better able to discriminate between participants with high versus low risk of CVD.

Mean daytime SBP according to ABPM will be defined in the following ways:

1. The mean of the first k readings after leaving the office setting and during the daytime, letting k = 2, 3, …, 20
2. The mean of a random set of k readings during the daytime, letting k = 2, 3, …, 20.

In total, we will assess 38 different definitions of daytime SBP according to ABPM. Using the definitions where 2 SBP measurements are sampled, we will use natural cubic splines to model a non-linear relationship between daytime SBP and CVD events, and formally test for non-linearity using the Wald F statistic. If these tests identify a non-linear relationship, we will categorize daytime SBP into discrete groups based on recommendations from the 2017 ACC/AHA BP guideline. Otherwise, we will model daytime SBP as a continuous variable and estimate hazard ratios for CVD according to a 10 mm Hg increase in daytime SBP.

**10.**  **References:** (Maximum 15)

1. Dadlani A, Madan K, Sawhney JPS. Ambulatory blood pressure monitoring in clinical practice. *Indian Heart J.* 2019;71(1):91-97.

2. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens.* 2013;31(9):1731-1768.

3. Verdecchia P, Reboldi G, Porcellati C, et al. Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects. *J Am Coll Cardiol.* 2002;39(5):878-885.

4. Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med.* 2003;348(24):2407-2415.

5. Yang WY, Melgarejo JD, Thijs L, et al. Association of Office and Ambulatory Blood Pressure With Mortality and Cardiovascular Outcomes. *JAMA.* 2019;322(5):409-420.

**PART II.  AUTHOR CONTRIBUTIONS**

**11.**  Have all co-authors reviewed and approved this document?   **X**   Yes (Required)

**12.**  Does the lead author (or designee) agree to present findings at a JHS Colloquium**?**

or Seminar?        **Yes** (required)

# PART III.  ADDITIONAL INFORMATION

# 13. Is this manuscript proposal based on an Ancillary Study? \_\_\_\_\_ Yes \_\_X\_­\_ No

# If yes, please provide the ASC # .

**14.**  **Type of Study:**

\_ **X**      Full Cohort                   Family Study           Sub-Study

\_      Ancillary Study           Case Control           Other (list):

**15.**  **Type of Data:**

\_  X    Longitudinal           Cross-Sectional         Other (list):

**16.**  **Location of Statistical Analysis:**

\_\_     Central (by Jackson Heart Study Staff)

\_**X**      Local (list site); **University of Alabama (Vanguard site)**

**17.** **Genetic Information:**

**a.** Do you propose use of data from a participant’s DNA?       Yes (see b)    **X**    No

**b**.   If yes, for a primary aim or secondary aim of JHS? (Please check one or both)

       Primary Aim (heart, vascular disease)       Secondary Aim (other conditions)

**18.**  **Conflict of Interest**

**a.** Are these analyses to involve a for-profit corporation?  \_\_\_\_\_Yes \_\_**X**\_\_No

**b**. Do you or any member of your Writing Group intend to patent any process, or

aspect of outcome from these analyses?  \_\_\_\_\_\_Yes    \_\_\_ **X**\_\_\_\_No

**19.**  **Data Sharing Agreement**

Has the Lead Author and any co-authors who will have direct access to JHS

data signed the JHS Data Sharing Agreement?      **Yes** (Required)

**20.**  **JHS Manuscript Overlap**

The Lead Author is responsible for reviewing the manuscript list on the JHS website http://jhs.jsums.edu/jhsinfo, listing the JHS manuscripts / manuscript proposals that are similar to the one he/she is proposing and justifying the differences and similarities. The lead author is encouraged to contact lead authors of the most related manuscript proposals for comments on the new proposal or collaboration.

**a**. Similar manuscripts / proposals : \_\_**X**\_\_\_No  \_\_\_\_\_\_Yes

**b**. If “yes”, list MS # title and Lead Author below)

**21. Manuscript Completion**

It is expected that the manuscript will be completed in less than one year. The manuscript proposal will expire if no manuscript is submitted for JHS review at the end of one year from the date of approval. If additional time is needed after one year, the Lead Author should request an extension from the Publications and Presentations Subcommittee.